IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **FERREE** **Serial No.: 10/630,445** Filed: July 30, 2003 For: METHODS FOR TREATING A DEFECT IN THE ANNULUS FIBROSIS (as amended)	Group Art Unit: 3731 Examiner: Uyen T. Ho

SECOND DECLARATION OF BRET FERREE, M.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Bret Ferree, M.D., do declare that:

1. I am a Board Certified Orthopedic surgeon specializing in spinal surgery. I am also a voluntary Assistant Professor at the University of Cincinnati. I received an M.D. from the University of Cincinnati College of Medicine (Cincinnati, Ohio) in 1986. I also completed a Spinal Surgery fellowship in the Department of Orthopedic Surgery at Tufts Medical School, New England Baptist Hospital (Boston, Massachusetts). In my capacity as an orthopedic surgeon specializing in spinal surgery, I have performed over 1,500 surgeries to repair disc herniations. I am the inventor of this application and President and Chief Executive Officer of Anova Corporation, assignee of the above-referenced application. I have a financial interest in this application.

2. I have reviewed U.S. Application Serial No. 10/630,445 and the pending claims. I understand the claims require the porous mesh or implant to be deployed so as to prevent escape of nucleus pulposus through the defect and that the proximal end of the porous mesh or implant is located distally beyond the outer layer of the annulus fibrosis.

3. I have reviewed the following references.

- Bao et al. U.S. Patent No. 6,224,630 "Implantable Tissue Repair Device"
- Flament et al. U.S. Patent No. 6,180,848 "Prosthesis Obturating Device for the Obturation of a Hernial Canal"
- Office Action dated January 22, 2007

4. The Office Action incorrectly takes the position that devices used to treat hernias in the wall of the abdomen can be modified to repair tears in the annulus fibrosis. Although inguinal hernias and herniated intervertebral discs share common underlying pathology -- both conditions begin with a tear in an outer layer of connective tissue, and soft tissue protrudes between the torn tissues, preventing healing of the torn tissue -- close analysis of the two conditions reveals substantial differences in anatomy, tissue healing, and biomechanics. The differences between the two conditions lead to very different design criteria for devices used to treat defects in the intervertebral disc and devices used to treat defects in the abdominal wall. Because of these very different design criteria those skilled in spinal surgery would reject the idea of treating tears in the intervertebral disc with abdominal wall hernia devices (such as described in Flament).

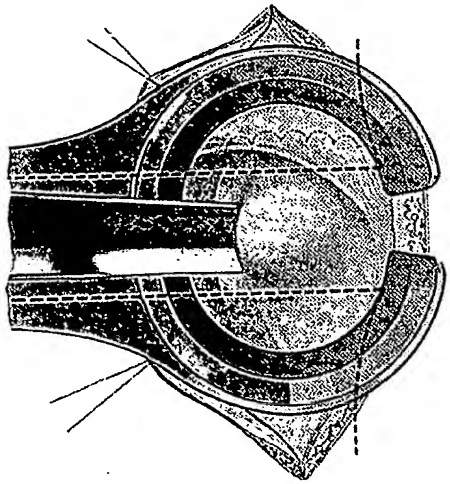
5. Figures 3 and 4 in Flament plainly show the proximal end of the porous mesh located outside and proximal the outer layer of the annulus fibrosis, not distally beyond the outer layer of the annulus fibrosis. This is the opposite of placing the proximal end of the porous mesh

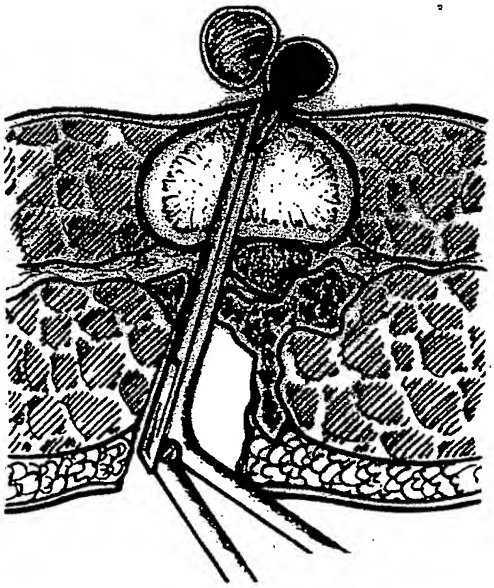
distally beyond the outer layer of the annulus fibrosis as required by the pending claims. Implementing these figures for treatment of disc herniation would therefore pose a danger to spinal nerves and will lead to severe pain, exacerbating the very condition this invention seeks to remedy.

6. Flament's Figure 2 likewise shows the proximal end of implanted material extending outside and proximal the outer layer of the annulus fibrosis, i.e., not distally beyond the outer layer of the annulus fibrosis. I understand the Examiner believes it would be obvious to reposition the Flament implant so the proximal end of mesh **1** is located distally beyond the outer layer of the annulus fibrosis. This belief is incorrect because Flament requires sutures on the base of "conical part **1**" to hold the porous mesh in place within the "canal," the aperture of the defect. Flament's Fig. 2 device, without sutures, would extrude into the spinal canal within hours of its insertion into an intervertebral disc. The suture method taught by Flament, may delay such extrusion. Although these sutures will ultimately fail to hold "conical part **1**" in place within an intervertebral disc for reasons explained below (and therefore Flament's device would be inoperative if used as suggested), the teaching to use sutures would require placement of the porous mesh outside and proximal the outer layer of the annulus fibrosis.

7. As a matter of surgical technique, it is very difficult to apply sutures even at the outer surface of an annulus fibrosis. This difficulty arises because extraordinary skill is required to manipulate a needle and suture through small spaces that access the spine. Exposure of annulus fibrosis tissue surrounding a tear in the annulus fibrosis is much more difficult than exposing the abdominal wall. Spinal surgeons must enter the spinal canal to access tears in intervertebral discs. Such access generally requires a laminotomy or hemi-laminectomy, i.e. removal of a portion of the lamina of a vertebra. The figure below left shows a laminotomy and

the limited window it provides into the spinal canal. The remaining portions of the vertebrae including the lamina, pedicles, facets, and the spinous processes act as a rigid frame around the window. The figure below right is an axial cross section of the spine. The illustration shows an instrument filling the entire laminotomy. The shaft of the instrument, just proximal to the middle of the shaft, is surrounded by bone (the lamina of the vertebra following laminotomy).





8. Surgeons do not have sufficient room to safely manipulate suture needles under the nerves through such limited exposure. This limited exposure allows only small changes in angle to maneuver the instruments. The instruments can be easily pushed deeper into the wound but can only be moved small distances in a cranial to caudal (i.e., head to toe) direction and in a left to right direction. Conversely abdominal surgeons like Flament have ample space to safely suture hernia repair devices because they (a) do not have to operate through a small window and under a sac of nerves, (b) have room to place the needle at a 90 degree angle relative to the axis of the defect, which placement facilitates manipulation of the needle, and (c) are not operating in a tunnel with a limited and rigid window.

9. The limited exposure described above for procedures taught in the present patent application is very intimidating. Injury to the nerves, dura, or veins can result in paralysis and death. The exposure is so intimidating that most Orthopedic surgeons who learn the technique during their training, choose not to perform surgery for herniated discs once they complete their training. The very limited exposure provided during surgical removal of disc herniations limits annulus fibrosis reconstruction techniques available to spinal surgeons. Spinal surgeons will not accept the suture technique used by our abdominal surgeon colleagues, and taught by Flament. Such suture techniques in such a small working area, surrounded by such important, easily damaged structures, would be extremely technically demanding. One would expect these suture techniques to have a very high complication rate including nerve injury, cerebral spinal fluid (CSF) leak, and failure of fixation from suboptimal suture placement. See, Exhibit 1 (Carragee et al JBJS 2003;85A;102-108, which reported results of surgical treatment of lumbar herniations in 187 consecutive patients and notes that eight patients (4%) experienced dural tears, at least 4 nerves were injured in Carragee's series (footdrop, bilateral L5/S1 nerve palsy, cauda equina syndrome, & increased sciatica)). Spinal surgeons cannot use the technique taught by Flament.

10. Flament's device must be fastened at multiple areas around the circumference of part **1**. It is, to my knowledge, almost impossible to manipulate a needle and suture *within* the canal so as to apply sutures to the edges that define the aperture of the defect. This technique would require manipulating the needle in a still smaller space than the rigid window described above, a space that is hidden from view because this space is within the edges of the defect. Such a technique, however, would be required if the proximal end of mesh **1** were placed distally beyond the outer layer of the annulus fibrosis, as the Examiner suggests. The small size of the slit-like opening will not permit surgeons to visualize the walls of the aperture nor to properly

place sutures through an obturator portion of a device and the walls of the aperture if the proximal portion of the device is placed distal the outermost layer of annulus fibrosis. Thus, if a spine surgeon sought to apply Flament to treatment of disc herniation (which they would not because Flament's device is designed for inguinal hernias), the skilled spine surgeon would understand Flament to require placement of the porous mesh outside and proximal the outer layer of the annulus fibrosis to allow for suturing.

11. Moreover, the Flament device will fail if implemented as proposed within an aperture in the intervertebral disc because it will protrude or extrude and therefore cause nerve injury. As noted in my previous declaration, intradiscal pressures are generally above 750 mmHg with normal activity and can be as high as 2.3 MPa (17,251 mmHg). See, Exhibit 2 (Wilke et al., "New *In Vivo* Measurements of Pressure in the Intervertebral Disc in Daily Life," Spine:24(8): 755-62, Table 1 (1999)); see also, Exhibit 3 (Einhorn, "Stability of a Mechanical Barrier Used to Seal Annular Defects." (Poster) Global Symposium on Motion Preservation Technology, Spinal Arthroplasty Society. New York (May 4-7, 2005) "intradiscal pressures up to 330 psi have been reported") Intradiscal pressures therefore exceed intra-abdominal pressures (150 mmHg) by a factor of 6-115. The high intradiscal pressure will cause the Flament device to protrude, or more likely, extrude into the spinal canal, causing symptoms similar to or worse than the bulging or herniated disc that Bao intends to treat. The extruded device will cause adhesions, require surgical removal, and may cause permanent nerve injury.

12. Flament's device is designed to resist a maximum pressure of 150 mmHg because it is designed for use in repair of inguinal hernias. Intradiscal pressures, which can be as high as 17,251 mmHg, will therefore flatten cone **2** (Figure 1 below). Flattening of cone **2** forces the apex of part **1** toward the spinal canal. Migration of the apex of part **1** towards the spinal canal

forces at least a portion of part **1** into the spinal nerves. Figure 1 below shows compression of the spinal nerves by part **1**.

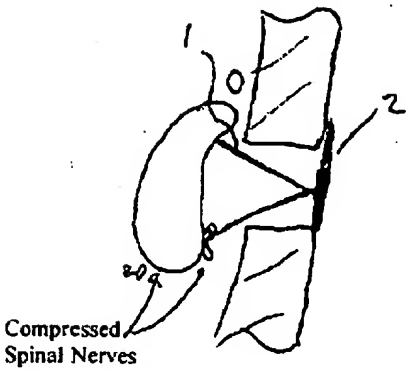


Figure 1

13. Flament teaches suturing the base of part **1** to the outer layers of tissues that surround the hernial canal. See, Flament at Fig. 2. Suturing the base of part **1** to the outer few layers of the annulus fibrosis adjacent to the aperture will not prevent protrusion or extrusion of the device. Figure 2A below shows one way part **1** may be sutured to the annulus fibrosis and yet protrude into the spinal nerves. Pressure from the nucleus pulposus causes deformity and migration of cone **2**. Migration of cone **2** deforms part **1**. Figure 2B below shows a second way a sutured part **1** may protrude into the spinal nerves. Suture tear would occur because Flament's suture technique, even if technically possible, would not be strong enough to retain a repair device. Flament's suture fixation technique, if used in an intervertebral disc, would require suture of the device to the thin portion of annulus fibrosis around the fissure, an area typically comprised of severely weakened tissue. Sutures placed through only the thin portion of the annulus fibrosis would quickly tear through the tissue and allow extrusion of the device towards the spinal nerves because the annulus fibrosis tissue surrounding the aperture is weakened. Figure 2C below shows a third way that, despite suturing the base of part **1** to the annulus

fibrosis adjacent to the aperture, part **1** may protrude into the spinal nerves. The tensile strength of mesh used to construct hernia repair devices, such as Flament's device, is not adequate to resist the high pressure within the intervertebral disc.

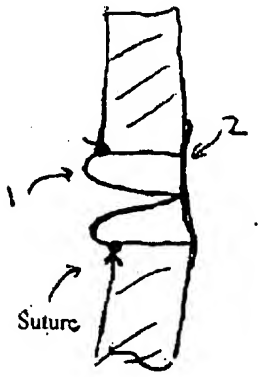


Figure 2A

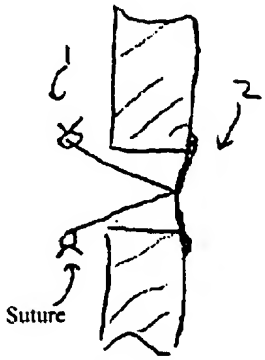


Figure 2B

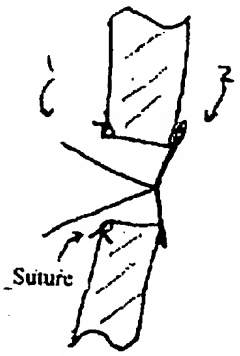


Figure 2C

14. Knot slippage can also cause part **1** to protrude into the spinal nerves despite suturing the base of part **1** to the annulus fibrosis adjacent to the aperture. The suture technique taught by Flament enables mesh devices to slide along the loop of suture much like a bead slides along a necklace. The mesh device will protrude further into the spinal canal (beyond the outer layer of the annulus fibrosis) as the device slides along the suture. Apreleva showed 40% of suture knots slip even when tied under ideal conditions. See, Exhibit 4 (Apreleva, American Academy of Orthopaedic Surgeons poster at 2002 annual meeting http://www.axya.com/ AAOS2002Poster.pdf). The failed knots allowed an average of 8 mm of elongation prior to failure. It should be noted the knots tested by Apreleva were tied under ideal conditions (which is not the case for spine surgeons). Thus, even it one could overcome the technical challenges of placing Flament's device in an intervertebral disc, an unacceptable percentage would migrate into the spinal nerves from knot slippage. While a few millimeters of migration of inguinal

hernia repair devices into the subcutaneous tissue is acceptable, a few millimeters of migration of intervertebral disc repair devices is unacceptable.

15. A more probable outcome from attempted use of Flament's device for repair of a herniated disc is extrusion of the entire device into the spinal canal. Hernia repair devices, such as the device taught by Flament sometimes extrude and migrate when the device is subjected to the low intra-abdominal pressure. As noted previously, given the high pressure within the intervertebral disc, spinal surgeons would expect a spinal version of the Flament device to extrude more frequently than similarly designed hernia repair devices. Such a complication would be catastrophic for the surgeon and the patient because it would cause severe pain and may cause permanent nerve injury (including permanent bowel, bladder, and sexual dysfunction).

16. Extrusion of the device, or protrusion of most of the device, would cause a condition worse than the herniated nucleus pulposus Bao intends to treat. High pressure from the nucleus pulposus would likely invert Flament's cone **2**. The pressure would force the apex of cone **2** into the aperture in the intervertebral disc. Cone **2** would thus change from concave to convex relative to the nerves in the spinal canal (Figure 3A below). Continued pressure from the nucleus pulposus will drive the apex of cone **2** into the apex of part **1**. Pressure from cone **2** on part **1** forces part **1** further into the spinal nerves (Figure 3B below). For these reasons, suture fixation of part **1** to the intervertebral disc would fail, allowing the entire device to extrude into the nerves (Figure 3C below).

Figure 3A

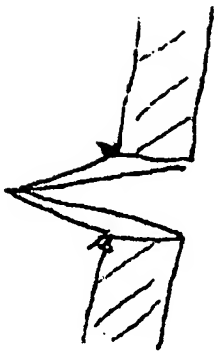


Figure 3B

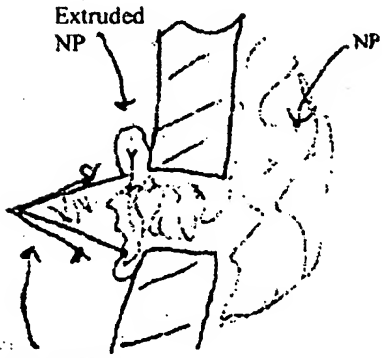
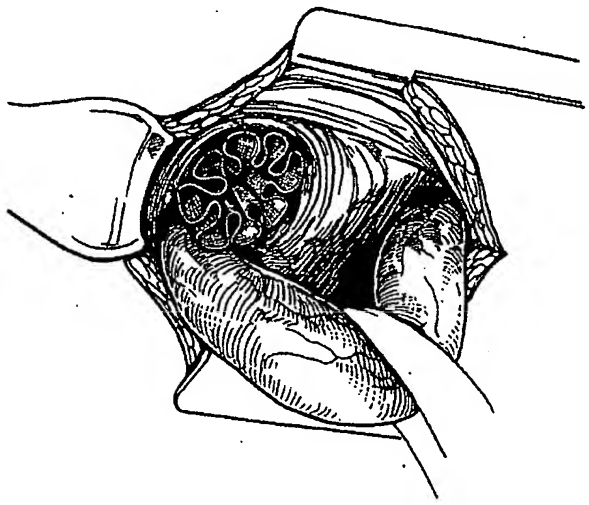


Figure 3C

17. Flament's device and the method Flament uses to insert and fasten the device would therefore lead to unacceptable nerve injuries. The figure below is a view of the external orifice of the hernia canal in an abdominal hernia. The obturator portion of a hernia repair device (like part **1** of Flament's device) was sutured to the superficial orifice of the abdominal hernial canal.



18. If such a technique was used to fasten a similar device to an aperture in the intervertebral disc, the device would lie against the spinal nerves. Figure 4A below is a posterior view of a coronal cross section of a portion of the spine with overlying nerves removed to expose

the spine. A Flament device has been sutured into an aperture in the intervertebral disc. Figure 4B below is a coronal cross section of the same portion of the spine showing nerves and the thecal sac (dotted area of the drawing) that lie directly over the exposed portion of part **1** of Flament's device. Figure 4C is an axial cross section of an intervertebral disc with Flament's device implanted. The device contacts the nerves.

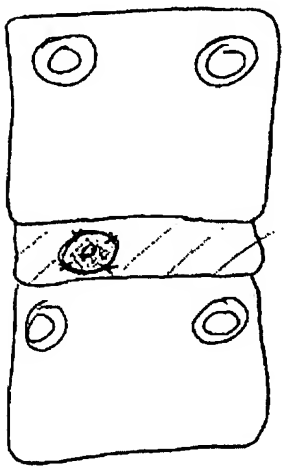


Figure 4A

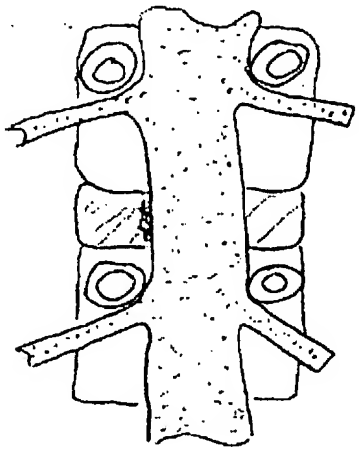


Figure 4B

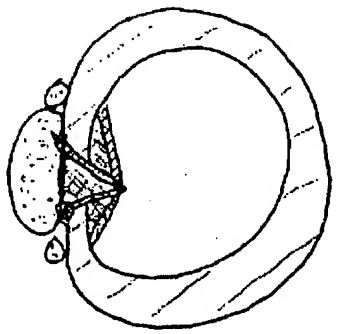


Figure 4C

19. For abdominal hernia repair, there is reported a 7.6% incidence of late postoperative pain after inguinal herniorrhapy, which is attributed to contact between the frayed nerves and the polypropylene mesh. See, Exhibit 5 (Starling, J.R. Chapter 112. "Abdominal Wall Hernias" Abdominal Wall Hernias Principles And Management. p. 734, second column, Bendavid R. et al., ed. Springer-Verlag New York, 2001). Hernia repair mesh can cause serve damage to other tissues that contact the mesh. Spinal surgeons would expect a still higher incidence of nerve related problems with use of a Flament device in an intervertebral disc. Spinal surgeons would also expect more serve consequences of spinal nerve injuries than with injury of nerves in abdominal hernia repair. Only a few nerves course through the area of abdominal hernia defects. Conversely, all the nerves to a patient's legs, anal sphincter, urinary

bladder, and genitalia course over the intervertebral disc. Injury to such nerves can result in severe pain, paraplegia, loss of bowel control, loss of bladder control, and loss of sexual function. The invention taught in the present application prevents such injuries to the spinal nerves. It does so by positioning the proximal end of the porous mesh or implant distally beyond the outer layer of the annulus fibrosis and by expanding the porous mesh or implant radially by reducing the length between the distal and proximal ends to ensure the proximal end is located distally beyond the outer layer of the annulus fibrosis. The intact layers of annulus fibrosis between the porous mesh and the spinal nerves prevent adhesions between the mesh and the spinal nerves.

20. Therefore, a skilled spine surgeon would have rejected any proposed use of the Flament device for repair of a herniated disc because the Flament device would protrude or extrude and therefore cause nerve injury if implemented as proposed within an aperture in the intervertebral disc.

21. I further declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent and application involved in the present proceedings.

Dated: 2/6/07

Bret Ferree, M.D.